

Physiology in Perspective: Physiology Provides Insight into Health

I'm a physiologist, so I have no excuse. I know that exercise is good for me, but all too often I neglect physical activity for other pursuits, sitting at my desk for hours working on my computer. I know to get up and move around, to become more active. Sound familiar? Like so many of us, my priorities are wrong, so I write editorials to remind myself. But we have been reminded over and over again and should all remember that "it is health that is real wealth and not pieces of gold and silver" (Mahatma Gandhi). Physiology provides us with the insight necessary for health and well being—we should pay more attention! In this issue of *Physiology*, we explore the link between physiology and all aspects of health. The very first article should be convincing in this respect, showing the link between physical activity, cognition, and mental health, with the take home message: "go run; it clears the mind."

We all know that exercise is beneficial for our general health (e.g., prevention of hypertension, heart disease, Type 2 diabetes, metabolic syndrome, osteoporosis, and metastatic diseases), but what is less appreciated is the beneficial effect of physical activity for brain function. Studies in rodents and humans indicate that exercise improves cognition and mood, might delay or prevent age-related memory decline, and can aid recovery from brain damage caused by injury or disease. Rodent studies have led to insight into the underlying mechanisms. Voluntary wheel running increases the production of new neurons (neurogenesis), neurotrophins, neurotransmitters, and angiogenesis in the hippocampus, a brain area important for learning and memory. In addition, running alters the development and function of new neuronal circuitry. In their review (4), Vivar and van Praag describe their studies showing that changes in the hippocampal neuronal network occur after only 1 wk of voluntary wheel running in young adult male mice. They found that this neural plasticity is

mainly attributable to modifications in glutamatergic neurotransmission onto newly born hippocampal neurons. They also show that longer periods of wheel-running activity (1 mo or more) increase input to new hippocampal neurons from multiple brain areas important for learning and memory (entorhinal cortex, septum, and mammillary nuclei). Interestingly, these same brain areas are also considered to be vulnerable in normal aging and neurodegenerative diseases.

For decades, it been known that skeletal muscles express large amounts of membrane ClC-1 chloride channels. Based on studies showing that loss of ClC-1 channel function leads to hyperexcitability and ensuing myotonia with spontaneous muscle activation, the general accepted concept was that the role of ClC-1 channels was to provide large resting conductance for Cl⁻, thereby reducing skeletal muscle fiber excitability to levels where there is no generation of spontaneous action potentials. However, detailed analysis of the importance of the resting membrane Cl⁻ conductance suggests that conductance can be substantially reduced before muscles become myotonic. In their review (2), Nielsen and colleagues take this a step further by demonstrating that the opening of the ClC-1 channels is highly regulated in working skeletal muscles and that this does not cause myotonia but rather serves to maintain muscle excitability and, thus, function. Thus, in their review, the authors suggest a completely new physiological role for the ClC-1 channels in muscle. In this concept, a downregulation of the ClC-1 channel opening in active muscles provides an explanation for why active but not resting muscles can tolerate large elevations in extracellular K⁺ that can take place during strenuous exercise. It also explains why accumulation of lactic acid under some circumstances may be protective against fatigue instead of causing fatigue. Obtaining a better understanding of fatigue mechanisms is relevant

for many work and exercise scenarios but may also be particularly important to understand and treat the reduction in muscle function that occurs in association with many neuromuscular diseases.

The conventional view of sodium-glucose-linked transporter (SGLT) proteins is that they are very important in the intestinal absorption of sugar from the diet and prevention of glucose loss in the urine. Such a functional role is apparent from SGLT mutations that cause glucose and galactose malabsorption and glucosuria. In their review (5), Wright and colleagues discuss recent studies that have uncovered a variety of unexpected functions for these transport proteins. SGLTs are members of a gene family that include a protein responsible for iodide accumulation in the thyroid gland, and are members of a structural family of proteins that include those responsible for the accumulation of neurotransmitters in the nervous system. There is evidence that these diverse transport proteins work by a very similar mechanism. SGLTs also behave as water transporters in the gut and glucose sensors throughout the body. Surprisingly, SGLT inhibitors provide an approved new therapy to treat Type 2 diabetes. SGLTs are expressed in pancreatic, prostate, and brain cancers, and there is preliminary evidence that SGLT inhibitors may be used to treat cancer. Recent studies demonstrate that SGLT1 is expressed in activated T-lymphocytes and that it plays an important role in the defense against infection. Finally, there is emerging evidence that SGLT1 in uterine tissue is important in maintaining normal fetal growth and development, and that SGLT1 deficiency in women may predispose them to early pregnancy failure. Further research is needed to answer the many unresolved problems in the field of SGLT biology and to contribute to new therapies for a wide variety of diseases.

The mammalian vascular system consists of two closely associated and functionally specialized networks: the circulatory and the lymphatic vasculature. Both vasculatures are highly branched and lined by endothelial cells. The lymphatic vasculature is important for fluid homeostasis, immune surveillance, and lipid absorption. It is also the main route for metastatic cells to

spread in the body, and inflammation-defective lymphatics can lead to lymphedema and other associated disorders. In their review (1), Ma and Oliver discuss newly discovered functional roles for the lymphatic vasculature in cardiovascular disease, glaucoma, cholesterol and salt regulation, metabolism, obesity, and neurological disorders. Importantly, it also has been shown that lymphatic endothelial cells (LECs) remain plastic throughout life and that their fate is reprogrammable. LEC fate manipulation could lead to therapies for a variety of pathological conditions, such as inflammation, tumorigenesis, and tissue injury. However, the extent and precise role of LEC plasticity remains to be defined before novel, cell-based therapies for vascular diseases can be developed.

Lactic acid is no longer regarded as merely a dead-end product of glycolysis.

It has become clear that lactic acid is a signaling molecule and a powerful regulator in multiple conditions of health and disease, including energy regulation, immune modulation, memory formation, wound repair, ischemic tissue injury, and cancer progression. In their review (3), Sun and colleagues discuss lactic acid transport, signaling, and functions in several pathophysiological processes. Although lactate administration to wounds likely promotes healing, in cancer it enhances metastasis. As such, it is a double-edged sword, with the potential to work for or against health. Although advances have been significant, further research and a better understanding of the functions and regulations of lactic acid can elucidate ways to exploit its influences and benefit patient care. ■

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